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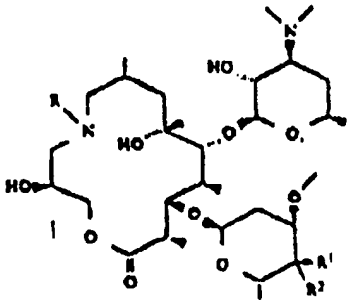
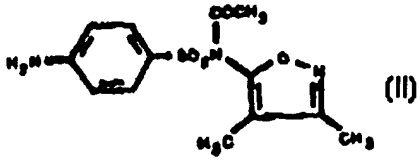
With amended claims.

(54) Title: 10-AZA-9-DEOXO-11-DEOXY-ERYTHROMYCIN A AND DERIVATIVES COMBINED WITH SULFISOXAZOLE



(I)



(II)

(57) Abstract

Pharmaceutical compositions of an erythromycin derivative combined with sulfisoxazole according to structural formulas (I) and (II) where R is hydrogen; C_1-C_{10} alkylcarbonyl, or substituted C_1-C_{10} alkyl wherein the substituent is amino or cyano; R^1 and R^2 are independently hydrogen, hydroxyl or amino; and the pharmaceutical salts and esters thereof.

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APPLICATION

Of

CHRIS PLATT

For

UNITED STATES LETTERS PATENT

On

10-Aza-9-Deoxo-11-Deoxy-Erythromycin A and Derivatives Combined with Sulfisoxazole

TITLE: 10-Aza-9-Deoxo-11-Deoxy-Erythromycin A and Derivatives Combined with Sulfisoxazole

BACKGROUND OF THE INVENTION

Field Of The Invention

The present invention relates to a novel group of chemical compounds providing antibacterial activity, and which are useful in the therapy of bacterial infections in mammals. More specifically, the invention relates to compositions including the derivatives of the well-known antibiotic, erythromycin A.

Description of Related Art

The related art includes:

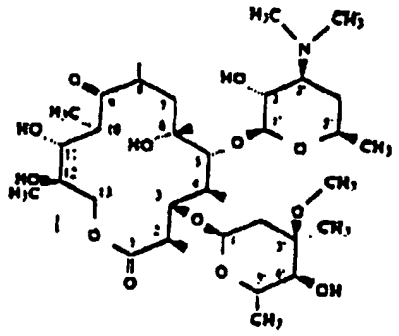
Tarpay et al, Antimicrobial Agents and Chemotherapy, Vol. 22, No. 1, pages 145-147 (1982).
Hughes et al., J. of Infectious Diseases, Vol. 170, No. 1, pages 906-911, (1994).
Doern et al., Antimicrobial Agents and Chemotherapy, Vol. 32, No. 2, pages 180-185 (1988).
U. S. Patents:

4,328,334 to Korbrehel et al	4,464,527 to Bright et al
4,465,674 to Bright et al	4,492,688 to Bright et al
4,512,982 to Hanske et al	4,517,359 to Kobrehel et al
4,526,889 to Bright et al	4,518,590 to Hanske et al
4,886,792 to Djokic	4,957,905 to Hunt et al

SUMMARY OF THE INVENTION

The erythromycin derivatives act by binding to the 50S ribosomal subunit of susceptible microorganisms and, thus, interfere with microbial protein synthesis. Nucleic acid synthesis is not affected. The sulfisoxazole inhibits bacterial synthesis of dihydrofolic acid by preventing the

condensation of the pteridine with para-aminobenzoic acid through competitive inhibition of the enzyme dihydopteroate synthetase. After absorption the erythromycin derivative is largely bound to plasma proteins and readily diffuses into most body fluids. Rapid distribution of erythromycin derivative into tissues and high concentration within cells results in higher concentrations in tissues than in serum or plasma. Erythromycin derivative seems to concentrate in fibroblasts and phagocytes as demonstrated by in vivo incubation techniques. Such derivatives are modifications of the well-known antibiotic, erythromycin A, having the following structure:



The erythromycin derivatives of the present invention relate to the compounds of the following structure and derivatives thereof, which form a novel class of 14-membered azalides characterized in that the heterocyclic nitrogen atom is situated at the 10 position. The inventive step in the present invention is that these compounds are combined with sulfisoxazole for enhanced antibacterial activity. The present invention provides for novel pharmaceutical compositions and methods for their use as antibacterial agents.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT

An important challenge in regards to antibiotics, is how to avoid the problem of pathological resistance to these medications. By combining two different antibiotics, each having different mechanisms of action, but which work synergistically together this problem can be overcome. The present invention stems from the discovery that certain erythromycin derivatives are easily

tolerated by patients without causing gastrointestinal disturbances. Additionally when combined with sulfisoxazole, resistance to Enterococcus Faecalis, methacillin-resistant stapylococci, and erythromycin resistant gram-positive strains is achieved. The inventive combination provides protection from a greater antibacterial spectrum then either erythromycin or sulfisoxazole alone. Thus, this new invention not only saves lives by providing a combination that overcomes medication resistance but is more easily tolerated without stomach upset and vomiting; side effects experienced by many people taking erythromycin alone.

Specifically the basis for the present invention is the pharmaceutical composition of an erythromycin derivative combined with acetylsulfisoxazole according to the structural formulas shown in Claim 1 below, where R is hydrogen; C1-C10 alkylcarbonyl, or substituted C1-C10 alkyl wherein said substituent is amino or cyano; and R1 and R2 are independently hydrogen, hydroxyl or amino; and including the pharmaceutical salts and esters thereof. Chemically acetylsulfisoxazole is N-(3,4,-Dimetly-5-isoxazole)-N-sulfanylactamide. Sulfisoxazole, where the acetyl group is replaced by H is an alternative substitution in the invention. Alternative possibilities for the erythromycin derivative include, but are not limited to, the structural formulas as shown in either Claim 3 where R is methyl, R^1 is H and R^2, in Claim 5 where R is ammino alkyl carbonyl, R^1 is H and R^2 is OH, and in Claim 6 where R is cyano, R^1 is an ammino group, and R^2 is H.

In an alternate embodiment, the composition of the present invention may be formulated wherein the erythromycin derivative has the general structural formula as shown below in Claim 2, including the pharmaceutically acceptable salts, esters and metal complexes thereof, wherein R^1 is hydrogen, C1-C10 alkyl carbonyl or unsubstituted or substituted C1-C10 alkyl wherein the substituent is amino or cyano; R^2 and R^3 are hydrogen; R^2 and R^3 together are oxo; R^4 is hydrogen or C1-C10 alkylcarbonyl; R^5 and R^6 are independently hydrogen, hydroxy or amino; R^5 and R^6 together are oxo or oximino; R^7 and R^8 are independently hydrogen, C1-C10 alkyl or phenylsulfonyl; R^9 is hydrogen, or C1-C10 alkylcarbony, and R^{10} is hydrogen. Examples of operable substitutions for the nine variables include the following:

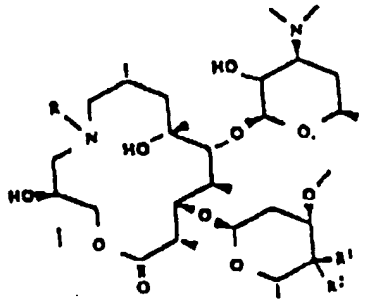
R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8	R^9
CH3	H	H	H	H	OH	H	H	H
CH3	H	H	H	H	OH	CH3	CH3	H
CH3	H	H	CH3	H	OH	H	H	H

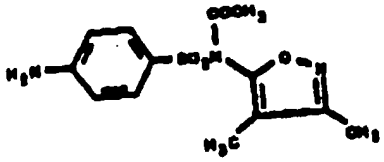
In formulating the combination of the present invention it has been found that the mixture ratio by weight, of erythromycin to sulfisoxazole, may range from 100:1 to as much as 1:1, and even trace amounts of sulfisoxazole may be operative. The preferred ratio is 100:38. The erythromycin and sulfisoxazole are prepared following standard laboratory procedures and processes that all competent workers in the field of the present invention will know.

The various alternative formulations of the present invention may take the form of a compressed pill, a powder in an easy to swallow caplet, or even as a fluid dissolved in a liquid such as water. In all cases, the formulation is to be taken orally.

CLAIMS

1. A pharmaceutical composition of an erythromycin derivative combined with acetylsulfisoxazole according to the structural formulas:





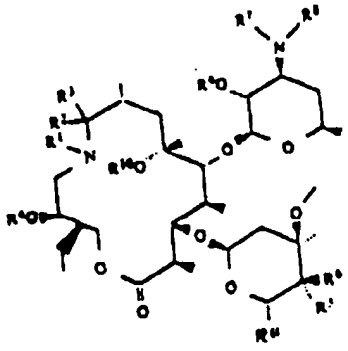
where R is hydrogen;

C1-C10 alkylcarbonyl, or substituted C1-C10 alkyl wherein said substituent is amino or cyano;

R1 and R2 are independently hydrogen, hydroxyl or amino;

and the pharmaceutical salts and esters thereof.

2. A pharmaceutical composition of a erythromycin derivative combined with acetylsulfisoxazole according to the structural formula:



and the pharmaceutically acceptable salts, esters and metal complexes thereof, wherein

R^1 is hydrogen,

C1-C10 alkylcarbonyl or unsubstituted or substituted

C1-C10 alkyl [where] wherein said substituent is amino or cyano;

R^2 and R^3 are hydrogen;

R^2 and R^3 together are oxo;

R^4 is hydrogen or C1-C10 alkylcarbonyl;

R^5 and R^6 are independently hydrogen, hydroxy or amino;

R^5 and R^6 together are oxo or oximino;

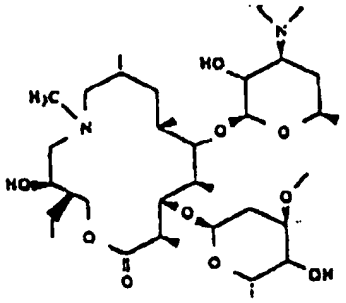
R^7 and R^8 are independently hydrogen, C1-C10 alkyl or phenylsulfonyl;

R^9 is hydrogen, or C1-C10 alkylcarbony,

R^{10} is hydrogen, and

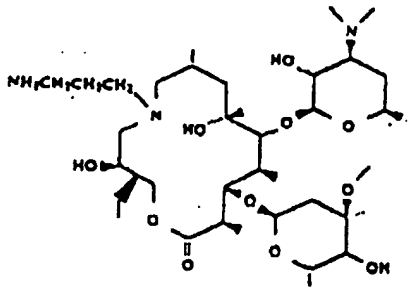
R^{11} is hydrogen or acetyl.

3. The composition as claimed in claim 1, wherein the erythromycin derivative has the structural formula:



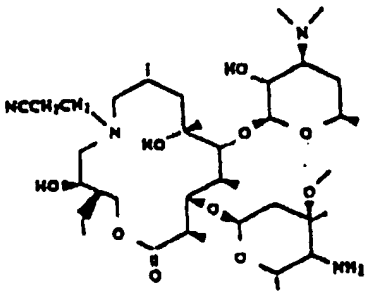
wherein R is methyl, R^1 is H and R^2 is OH.

4. The composition as claimed in claim 1, wherein the erythromycin derivative has the structural formula:



wherein R is amino alkyl carbonyl, R^1 is H and R^2 is OH.

5. The composition as claimed in claim 1, wherein the erythromycin derivative has the structural formula:

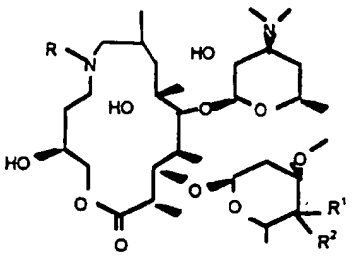


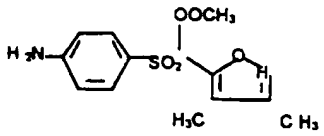
wherein R is cyano, R^1 is an amino group, and R^2 is H.

AMENDED CLAIMS

[received by the International Bureau on 12 August 1997 (12.08.97); original claims 1-5 replaced by amended claims 1-5 (3 pages)]

1. A pharmaceutical composition of an erythromycin derivative combined with acetylsulfisoxazole according to the structural formulas:



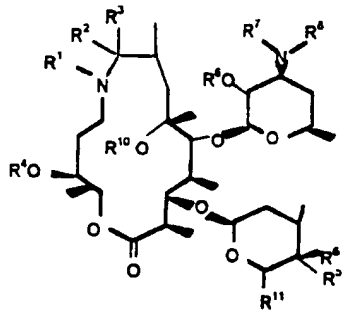


where R is hydrogen;

C_1-C_{10} alkylcarbonyl, or substituted C_1-C_{10} alkyl wherein said substituent is amino or cyano;

R^1 and R^2 are independently hydrogen, hydroxyl or amino; and the pharmaceutical salts and esters thereof.

2. A pharmaceutical composition of a erythromycin derivative combined with acetylsulfisoxazole according to the structural formula:



and the pharmaceutically acceptable salts, esters and metal complexes thereof. wherein

R^1 is hydrogen,

C_1-C_{10} alkylcarbonyl or unsubstituted or substituted.

C_1-C_{10} alkyl [where] wherein said substituent is amino or cyano;

R^2 and R^3 are hydrogen;

R^2 and R^3 together are oxo;

R^4 is hydrogen or C_1-C_{10} alkylcarbonyl;

R^5 and R^6 are independently hydrogen, hydroxy or amino;

R^5 and R^6 together are oxo or oximino:

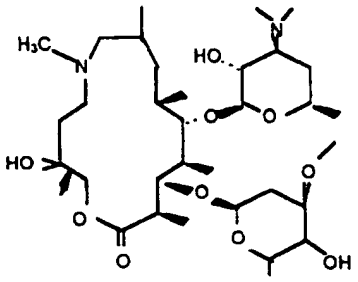
R^7 and R^8 are independently hydrogen. C_1-C_{10} alkyl or phenylsulfonyl;

R^9 is hydrogen. or C_1-C_{10} alkylcarbonyl,

R^{10} is hydrogen, and

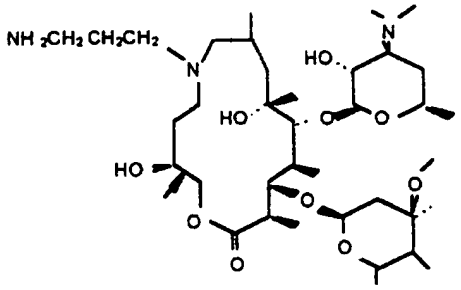
R^{11} is hydrogen or acetyl.

3. The composition as claimed in claim 1, wherein the erythromycin derivative has the structural formula:



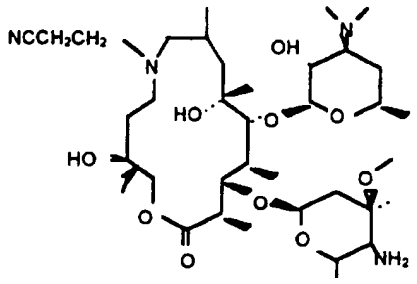
wherein R is methyl, R^1 is H and R^2 is OH.

4. The composition as claimed in claim 1, wherein the erythromycin derivative has the structural formula:



wherein R is amino alkyl carbonyl, R^1 is H and R^2 is OH.

5. The composition as claimed in claim 1, wherein the erythromycin derivative has the structural formula:



wherein R is cyano, R^1 is an amino group, and R^2 is H.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/04743

A. CLASSIFICATION OF SUBJECT MATTER
IPC(6) : A61K 31/70, 31/42
US CL : 514/29, 378
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 514/29, 378

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
none

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
cas-online, aps

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Antimicrobial Agents and Chemotherapy, Volume 22, Number 1, issued July 1982, Tarpay et al., "In Vitro Activity of Antibiotics Commonly Used in the Treatment of Otitis Media Aganist Streptococcus pneumoniae Isolates with Different Susceptibilites to Penicillin", pages 145-147, see the entire document.	1-5
Y	Antimicrobial Agents and Chemotherapy, Volume 32, Number 2, issued February 1988, Doern et al., "National Collaborative Study of the Prevalence of Antimicrobial Resistance among Clinical Isolates of Haemophilus influenzae", pages 180-185, see the entire document.	1-5

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/04743

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	The Journal of Infectious Diseases, Volume 170, Number 1, issued 1994, Hughes et al., "Relative Potency of 10 Drugs with Anti-Pneumocyctis carinii Activity in an Animal Model", pages 906-911.	1-5
Y	M. Windholz et al., "THE MERCK INDEX, AN ENCYCLOPEDIA OF CHEMICALS, DRUGS, AND BIOLOGICALS, TENTH EDITION", published 1983 by Merck & CO., Inc. (N.J.), page 16, see number 104.	1-5